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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,907	06/05/2001	Jon A. Weidanz	49890(48340)	3602
21874 7590 07/10/2007 EDWARDS ANGELL PALMER & DODGE LLP P.O. BOX 55874 BOSTON, MA 02205				
			EXAMINER SCHWADRON, RONALD B	
			ART UNIT 1644	PAPER NUMBER
			MAIL DATE 07/10/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/874,907

Applicant(s)

WEIDANZ ET AL.

Examiner

Ron Schwadron, Ph.D.

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 81,82,84-100,102-125 and 144-150 is/are pending in the application.
- 4a) Of the above claim(s) 84,87-100,103-123 and 125 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 81,82,85,86,102,124,144-150 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

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1. Applicant's election of Class I and P53 in the reply filed on 3/7/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). A request for an election of a single sequence of the claimed molecule with the aforementioned characteristics has not been made.

2. Claims 81,82,85,86,102,124,144-150 are under consideration.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration (the residence and PO address for Inventor Weidanz). See 37 CFR 1.52(c).

Applicant has indicated that a new declaration signed by Inventor Weidanz will be filed.

4. Applicant is required to update the status of all US patent applications disclosed in the instant application.

Applicant has indicated that this issue will be addressed via a substitute specification which will be filed.

5. Applicant is required to amend the specification to identify all sequences with the appropriate SEQ. ID. number.

Applicant has indicated that this issue will be addressed via a substitute specification which will be filed.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. The rejection of claims 81-83,85,86,124 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 6,534,633 for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 81,82,85,86,102,124,144-150 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a) There is no support in the specification as originally filed for the recitation of "alpha and beta variable chain covalently linked together by a second peptide linker". Regarding applicants comments, whilst claim 83 disclosed a heterodimeric molecule, it did not disclose a heterodimeric molecule containing a linker. Heterodimeric molecules are commonly joined via disulfide bonds (aka not containing a linker). Figure 11 discloses a linker between the c-terminus of a TCR and n-terminus of an Fv. It does not disclose a linker between an alpha and beta chain of a TCR. The cited passage of the specification, page 19 refers to the linker between the TCR and biologically active peptide. It does not disclose a linker between an alpha and beta chain of a TCR.

b) There is no support in the specification as originally filed for claim 144. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope in the context of any HLA molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

c) There is no support in the specification as originally filed for claim 145. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope in the context of HLA 2.1 molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

d) There is no support in the specification as originally filed for claim 146. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which contains any TCR which binds said p53 epitope in the context of any HLA molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

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e) There is no support in the specification as originally filed for the limitation of claim 147/148. The cited passage of the specification discloses said linkers between a TCR and a biologically active molecule, but does not disclose said linkers as used between an alpha and beta chain of a TCR.

f) There is no support in the specification as originally filed for the limitation of claim 149. The specification, page 19 discloses that "The linker is preferably predominantly comprises amino acids with small side chains, such as glycine, alanine and serine, to provide for flexibility.". Thus, the cited passage of the specification contains the additional limitation that the linker must provide for flexibility.

There is no support in the specification as originally for the scope of the claimed inventions (aka the claimed inventions constitute new matter).

10. Based on the Example 1 of the specification, the terms "TCR" and "alpha and beta chain TCR" are interpreting as encompassing TCR or TCR chains that contain the relevant variable domains, but do not necessarily contain constant domains or intact constant domains found in the naturally occurring TCR/ TCR alpha or beta chain. Example 1 refers to single chain TCR wherein the disclosed molecule lacks alpha chain constant regions.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. The rejection of claims 81-83,85,86,101,102,124 under 35 U.S.C. 102(b) as being anticipated by Bonneville et al. (US Patent 5,723,309) for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

13. The rejection of claims 81-83,85,86 under 35 U.S.C. 102(b) as being anticipated by Weidanz et al. (WO 99/18129) is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

14. The rejection of claims 81-83,85,86 are rejected under 35 U.S.C. 102(b) as being anticipated by Weidanz et al. (WO 98/39482) for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

15. The rejection of claims 81-83,85,86 under 35 U.S.C. 102(b) as being anticipated by Banerji et al. for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled. The Banerji reference (WO 96/13593) was of record in the PTO 1449 mailed 7/26/05

16. The rejection of claims 81-83,85,86,124 under 35 U.S.C. 102(e) as being anticipated by Weidanz et al. (US Patent 6,534,633) for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

17. The rejection of claims 81-83,85,86,124 under 35 U.S.C. 102(a) as being anticipated by Weidanz et al. (WO 00/23087) for the reasons elaborated in the previous Office Action is withdrawn in view of the amended claims and cancellation of claims that have been cancelled.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 81,82,85,86,102,124,144,145,147-150 rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309).

Weidanz et al. teach a soluble single chain alpha beta TCR wherein the Valpha and Vbeta chain are connected by a linker(see claims 1,2,4 and page 4, penultimate paragraph). The alpha beta chains of the TCR are covalently linked by the linker of claim 147 ((see page 24, last paragraph) wherein the optimal length would be determined via routine experimentation. The linker can contain the amino acids of claim 149 (see page 24, last paragraph). The TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 (see page 34, first paragraph). Weidanz et al. teach said TCR in a pharmaceutical (aka therapeutic) composition (see page 42). Weidanz et al. teach said TCR in a fusion protein containing an effector molecule wherein said effector is attached to the Valpha /Vbeta chain via an intervening C κ or C λ chain wherein said chain would function as a "peptide linker" (see claim 43). The "includes" of claim 148 is interpreted as equivalent in scope to "comprising". Weidanz et al. do not teach that the effector molecule is a cytokine. Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to

IL-2 (see column 3, lines 40-52 and column 2, last four paragraphs). Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). IL-2 is specific for recognition of an effector cells (immune cells expressing IL-2 receptor such as activated T cells). Bonneville et al. disclose that said TCR/IL-2 fusion proteins can be used to treat disease (see column 5, lines 57-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Weidanz et al. teach the claimed TCR fusion proteins except for use of IL-2 whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2. One of ordinary skill in the art would have been motivated to do the aforementioned because Weidanz et al. teach said TCR in a fusion protein containing an effector molecule whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2 and that said TCR/IL-2 fusion proteins can be used to treat disease.

20. Claim 146 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309) as applied to claims 81,82,85,86,102,124,144,145,147-150 above, and further in view of Theobald et al.

The previous rejection renders obvious the claimed invention except wherein the TCR binds the peptide of claim 146. Weidanz et al. disclose that the TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 (see page 34, first paragraph). Theobald et al. disclose HLA 2.1 antigen restricted CTL which contain TCR which bind the aforementioned peptide (see Table 1), where said CTL have the best lytic activity of the tested CTL (see Table 1). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except wherein the TCR binds the peptide of claim 146 whilst Weidanz et al. disclose that the TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 and Theobald

et al. disclose antiP53 HLA 2.1 antigen restricted CTL which contain TCR which bind the aforementioned peptide (see Table 1), where said CTL have the best lytic activity of the tested CTL (see Table 1). One of ordinary skill in the art would have been motivated to do the aforementioned because Weidanz et al. disclose that the TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 and Theobald et al. disclose antiP53 HLA 2.1 antigen restricted CTL which contain TCR which bind the aforementioned peptide where said CTL have the best lytic activity of the tested CTL.

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ron Schwadron, Ph.D.

Primary Examiner

Art Unit 1644


RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800 (600)